

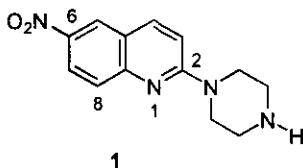
A NEW EFFICIENT SYNTHESIS OF 6-NITROQUIPAZINE

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Abstract - A convenient and regioselective synthesis of 6-nitroquipazine from hydrocarbostyryl in three steps is described. This synthetic route involved a nitration, a chlorination followed by aromatization, and an aromatic substitution reaction.

Our interest in developing new neurotransmitters, which have good affinity to serotonin transporter *in vivo*, has led us to synthesis of 6-nitroquipazine (**1**) derivatives. 6-Nitroquipazine has been known as one of the most potent and selective antagonist of 5-hydroxytryptamine (Serotonin or 5-HT) transporter *in vitro*^{1,2} and *in vivo*.^{3,4} Recently, a comparative molecular field analysis (COMFA) and pharmacological evaluation of quipazine, one of arylpiperazine, with a subtype of serotonin receptor, 5-HT₃, were reported.^{5,6}



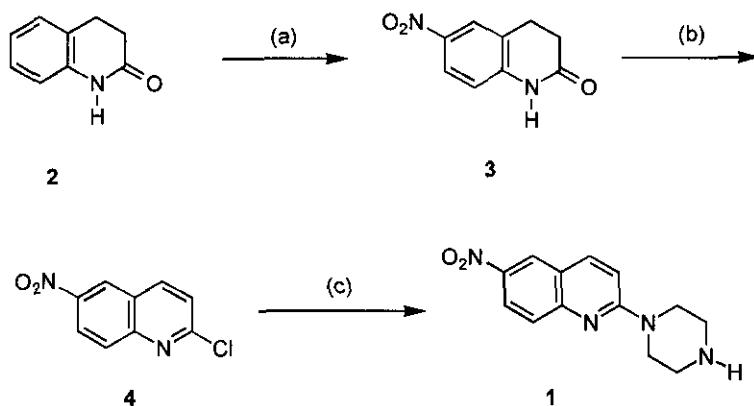
Even though 6-nitroquipazine has a good binding affinity toward 5-HT transporter, the studies of structure-activity relationship of its derivatives are not sufficient. Surprisingly, the regioselective synthesis of 6-nitroquipazine has not been reported. The only synthesis of 6-nitroquipazine itself was known as a patent by Hashimoto and Goromaru.⁷ This process, however, was neither regioselective nor efficient. The final process of this patent is a non-regioselective nitration of quipazine and requires the isolation of the 6-nitro derivative from mixture of nitroquipazines. In our experiment, the direct nitration of quinaldine provided a

mixture of 5-, 6-, 8-nitroquinolines in 71% yield with the ratio of 33:8:59 under the normal acidic nitration condition using conc. HNO_3 /conc. H_2SO_4 . Furthermore the synthetic route to 5-iodo-6-nitroquipazine reported by Mathis *et al.* is too inefficient and difficult to obtain the target molecule in good yield.⁸⁻¹⁰ We now report a new regioselective and efficient synthesis of 6-nitroquipazine (**1**).

Synthesis of quinolines containing electron-withdrawing groups in the aryl ring was required for the preparation of biologically active compounds. Unfortunately, many of quinoline routes - Combes,¹¹ Conrad-Limpach,¹² Skraup,¹³ Friedländer,¹⁴ and Pfitzinger synthesis¹⁵ - are largely affected by the nature of substituents, and electronic-withdrawing substituents are appreciably unfavorable for cyclization although electron-donating ones are preferable. In addition, there are limitations due to orientation of ring closure by either electron-donating or -withdrawing substituents on the ring.

As shown in Scheme 1, 6-nitroquipazine was prepared by three steps from a commercially available starting material, hydrocarbostyryl (**2**), in 82% yield.

Scheme 1. Synthesis of 6-Nitroquipazine from Hydrocarbostyryl.



Reaction conditions: (a) conc. H_2SO_4 , conc. HNO_3 , $-10\text{ }^\circ\text{C}$, 3 h; (b) DDQ, POCl_3 , benzene, reflux, 3 h; (c) (i) 1-piperazinecarboxaldehyde, DMF, reflux, 2 h; (ii) 4 M H_2SO_4 , $90\text{ }^\circ\text{C}$, 3 h.

This synthetic route involved a nitration of hydrocarbostyryl, a chlorination and aromatization in the presence of dichlorodicyanobenzoquinone (DDQ) with POCl_3 , and an aromatic displacement reaction with piperazine.

Nitration proceeded too fast to form a dinitrated side-product, 6,8-dinitrohydrocarbostyryl under the normal acidic nitration conditions using conc. HNO_3 /conc. H_2SO_4 with a desired mononitro

product, 6-nitrohydrocarbostyryl in 60% yield. Dilution of the acids with water and lowering the reaction temperature to $-10\text{ }^{\circ}\text{C}$ improved the yield of mononitro product (**3**) to 90%. 6-Nitrohydrocarbostyryl reacted with five equivalents of phosphorus oxychloride and one equivalent of chloranil in benzene to give 2-chloro-6-nitroquinoline (**4**) in 50% yield. But the yield was improved upto 96% when DDQ was used instead of chloranil. This process likely involves chlorination with POCl_3 and subsequent aromatization with DDQ. In order to confirm this aspect, the reaction was carried out under several different conditions. Upon treatment with only phosphorus oxychloride without DDQ, **4** was formed although in a low yield of 3% with consuming of all the starting material (**3**). On the other hand, when DDQ was used without POCl_3 , 6-nitro-2-quinolone was not formed and only the starting material (**3**) was recovered. 6-Nitrohydrocarbostyryl was treated with five equivalents of POCl_3 and 0.3, 0.4, 0.5, and 1.0 equivalents of DDQ in benzene to give 2-chloro-6-nitroquinoline (**4**) in 20, 37, 41, and 96% yields, respectively. 6-Nitroquipazine was obtained in 95% yield by aromatic nucleophilic substitution reaction of 2-chloro-6-nitroquinoline with five equivalents of 1-piperazinecarboxaldehyde in DMF under refluxing for 2 h, followed by refluxing with 4M H_2SO_4 for 1h to remove the carboxaldehyde protecting group.

Recently, we have reported the synthesis of hydrocarbostyryl as a major product in 90% yield by the Beckmann rearrangement of 1-indanone oxime using AlCl_3 *via* tosylate at from $-40\text{ }^{\circ}\text{C}$ to room temperature.¹⁶ While the yield of the Beckmann rearrangements of α -tetralone was higher than 65%, that of 1-indanone was only 20%, when polyphosphoric acid was used at $110\text{-}120\text{ }^{\circ}\text{C}$ for 10 min.

EXPERIMENTAL

Materials and methods. ^1H NMR and ^{13}C NMR spectra were obtained on a Gemini-200 (200 MHz, Varian) and are reported in ppm downfield from internal tetramethylsilane. Solvents and reagents were purchased from the following commercial sources: Aldrich, Kanto, Acris. Analytical TLC was performed with Merck silica gel F-254 glass-backed plates. Visualization was achieved by phosphomolybdic acid (PMA) spray reagent, iodine, or UV illumination. Flash chromatography was performed according to Still¹⁷ using Woelm silica gel (0.040-0.063 mm). MS were obtained on HP590 GC/MS 5972 MSD spectrometer.

6-Nitro-3,4-dihydro-2(1H)-quinolinone (3). After hydrocarbostyryl (1.00 g, 6.70 mmol) was dissolved in 20 mL of conc. H_2SO_4 , 5 mL of water was slowly added to the solution at $-10\text{ }^{\circ}\text{C}$. 61% HNO_3 (0.50 mL, 6.70 mmol) was added to the well-stirred solution dropwise at $-10\text{ }^{\circ}\text{C}$.

After the reactants were stirred for 10 min in a cooling bath, the reaction mixture was quenched by adding 50 mL of cold water carefully at rt. The resulting mixture was extracted with ethyl acetate (30 mL \times 5). The combined extracts were dried over sodium sulfate, and evaporated under reduced pressure. The 1.17 g (90%) of 6-nitrohydrocarbostyryl (**3**) and 0.065 g (5%) of 8-nitrohydrocarbostyryl were obtained by flash chromatography (CH_2Cl_2), both as pale yellow crystals: mp, 210.5-211.0 °C (EtOAc); IR (KBr) 3485, 3225, 3090, 2915, 1675, 1590, 1500, 1330 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3) δ 9.50 (br s, 1H), 8.09 (br s, 2H), 6.94 (d, $J = 9.4$ Hz, 1H), 3.09 (t, $J = 7.6$ Hz, 2H), 2.72 (t, $J = 7.5$ Hz, 2H); ^{13}C NMR (50 MHz, CDCl_3) δ 170.1, 141.6, 141.3, 122.5, 122.3, 122.2, 113.8, 28.2, 23.3; MS (EI) m/z (relative intensity) 192 (M^+ , 100), 164 (50), 134 (32), 117 (43), 91 (31), 77 (27). Anal. Calcd for $\text{C}_9\text{H}_8\text{N}_2\text{O}_3$: C, 56.25; H, 4.20; N, 14.58. Found: C, 56.45; H, 4.58; N, 14.70.

2-Chloro-6-nitroquinoline (4). To a solution of **3** (0.30 g, 1.56 mmol) and DDQ (0.35 g, 1.56 mmol) in 5 mL of benzene was added dropwise POCl_3 (0.71 mL, 7.8 mmol) at rt. The mixture was refluxed at 90 °C for 3 h, and then quenched by adding 20 mL of cold water. The mixture was neutralized with 4N NaOH, and extracted with ethyl acetate (20 mL \times 3). The combined extracts were dried over sodium sulfate, and evaporated under reduced pressure. 2-Chloro-6-nitroquinoline (**4**, 0.31 g, 96%) was obtained by flash chromatography (10% EtOAc/hexane) as pale yellow crystals: mp, 235.5-236.5 °C (EtOAc); IR (KBr) 3450, 3100, 3060, 1620, 1530, 1490, 1340 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3) δ 8.79 (d, $J = 2.6$ Hz, 1H), 8.51 (dd, $J = 9.2, 2.6$ Hz, 1H), 8.30 (d, $J = 8.8$ Hz, 1H), 8.16 (d, $J = 9.4$ Hz, 1H), 7.57 (d, $J = 8.8$ Hz, 1H); ^{13}C NMR (50 MHz, $\text{DMSO}-d_6$) δ 152.6, 148.3, 144.5, 140.8, 128.8, 125.0, 123.9, 123.3, 123.0; MS (EI) m/z (relative intensity) 208 (M^+ , 72), 162 (39), 150 (42), 127 (100), 100 (23), 74 (22). Anal. Calcd for $\text{C}_9\text{H}_6\text{N}_2\text{O}_2\text{Cl}$: C, 51.92; H, 2.42; N, 13.43. Found: C, 51.99; H, 2.42; N, 13.14.

6-Nitroquipazine (1). To a solution of **4** (0.44 g, 2.10 mmol) in 15 mL of DMF was added dropwise 1-piperazinecarboxaldehyde (0.53 mL, 4.20 mmol) at rt. The mixture was heated for 2 h at 110 °C, and cooled to rt. 4 M H_2SO_4 (40 mL, 160.00 mmol) was added to the mixture. The mixture was heated at 90 °C for additional 3 h, and then quenched by adding 30 mL of cold water, and basified with 4 N NaOH. The resulting precipitate was filtered and washed with water and hexane. The filtrate was dried in oven overnight to give 6-nitroquipazine (**1**, 0.52 g, 95%): mp, 181-183 °C (EtOAc); IR (KBr) 3330, 2940, 3010, 2620, 1490, 1320 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3) δ 8.46 (d, $J = 2.2$ Hz, 1H), 8.23 (dd, $J = 9.0, 2.2$ Hz, 1H), 7.90 (d, $J = 9.4$ Hz, 1H), 7.60 (d, $J = 9.4$ Hz, 1H), 7.01 (d, $J = 9.2$ Hz, 1H), 3.79 (m, 4H), 2.98 (m, 4H), 2.08 (br s, 1H);

^{13}C NMR (50 MHz, CDCl_3) δ 157.0, 149.9, 140.2, 137.0, 125.4, 122.6, 121.9, 119.4, 109.2, 44.3, 44.1.

ACKNOWLEDGMENTS

This research was supported by The Hallym Academy of Sciences, Hallym University, Korean Ministry of Education through Research Fund (No. BSRI-96-3443), and the Korea Science and Engineering Fund (No 97-03-01-01-5-L).

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